15:03:46 OCA PAD INITIATION - PROJECT HEADER INFORMATION 07/31/95

Active

Project #: G-33-X05 Cost share #: Rev #: 0
Center # : 10/24-6-R8611-0A0 Center shr #: OCA file #:
Work type : RES
Contract#: NP-912 Mod #: Document : GRANT
Prime #: Contract entity: GTRC

Subprojects ? : N CFDA:
Main project #: PE #:

Project unit: CHEMISTRY Unit code: 02.010.136
Project director(s):
WILLIAMS L D CHEMISTRY (404)894-8222

Sponsor/division names: AMERICAN CANCER SOCIETY / NEW YORK, NY
Sponsor/division codes: 500 / 081

Award period: 950701 to 970630 (performance) 970831 (reports)

Sponsor amount	New this change	Total to date
Contract value	180,000.00	180,000.00
Funded	180,000.00	180,000.00
Cost sharing amount		0.00

Does subcontracting plan apply ?: N

Title: DNA INTERCALATION

PROJECT ADMINISTRATION DATA

OCA contact: Jacquelyn L. Bendall 894-4820

Sponsor technical contact

LAURIE FISCHER
(404)816-1262

AMERICAN CANCER SOCIETY
GEORGIA DIVISION
2200 LAKE BOULEVARD
P.O. BOX 190429
ATLANTA, GA 31119-0429

Sponsor issuing office

(000)000-0000

Security class (U,C,S,TS) : U ONR resident rep. is ACO (Y/N): N
Defense priority rating : N/A N/A supplemental sheet
Equipment title vests with: Sponsor GIT X

Administrative comments -
INITIATION OF PROJECT. MAJOR CHANGES IN THE BUDGET REQUIRE PRIOR APPROVAL FROM THE SCIENTIFIC PROGRAM DIRECTOR.

CA8120

Georgia Institute of Technology
Office of Contract Administration
PROJECT CLOSEOUT - NOTICE

22-JAN-1998 14:54

Closeout Notice Date 22-JAN-1998

Project Number G-33-X05 Doch Id 36236

Center Number 10/24-6-R8611-0A0

Project Director WILLIAMS, LOREN

Project Unit CHEMISTRY

Sponsor AMERICAN CANCER SOCIETY/NEW YORK, NY

Division Id 6007

Contract Number NP-912 Contract Entity GTRC

Prime Contract Number

Title DNA INTERCALATION

Effective Completion Date 30-JUN-1997 (Performance) 31-AUG-1997 (Reports)

Closeout Action:	Y/N	Date Submitted
Final Invoice or Copy of Final Invoice	Y	
Final Report of Inventions and/or Subcontracts	Y	
Government Property Inventory and Related Certificate	N	
Classified Material Certificate	N	
Release and Assignment	N	
Other	N	

Comments

Distribution Required:	
Project Director/Principal Investigator	Y
Research Administrative Network	Y
Accounting	Y
Research Security Department	N
Reports Coordinator	Y
Research Property Team	Y
Supply Services Department/Procurement	Y
Georgia Tech Research Corporation	Y
Project File	Y

NOTE: Final Patent Questionnaire sent to PDPI

G-33-X05
#1 (Final)

Lay & Scientific Summaries
Due 8/31/97
G-33-X05

DNA Intercalation
American Cancer Society
Grant #NP-912
PI: Loren Dean Williams
School of Chemistry and Biochemistry

Lay Summary. Many clinically useful drugs act by binding to DNA, the genetic material. This family of drugs includes antiviral, antifungal, antitrypanosomal and especially anticancer agents. For example both adriamycin (used to treat solid tumors) and daunomycin (used to treat leukemia) bind to DNA. These drugs ultimately interfere with cellular machinery by which cells copy and process their DNA. The goal of our research is to understand, and to someday even predict, how these drugs bind to, and distort DNA. We are trying to address these issues on an extremely detailed level, by actually looking at the exact positions of individual atoms of DNA-drug complexes. To do this we use a technique known as x-ray crystallography. We grow crystals of DNA-drug complexes (not an easy process) and direct a beam of x-rays through the crystal. The beam of x-rays is scattered by the atoms of the crystal. By collecting and properly processing the scattered x-ray beam we can reconstruct the positions of the atoms of the DNA and of the bound drug molecule. The information we obtain is used to design new and better chemotherapeutic agents.

Scientific Summary. Our ultimate goal is structure-based drug design of DNA-binding anticancer chemotherapeutics. Structure-based drug design entails (1) detailed 3-D structures and analysis of inhibited complexes of target macromolecules, (2) solution affinity measurements, (3) biological screening, and (4) design and syntheses of new inhibitors.

DNA is a target of many clinically important chemotherapeutic agents. DNA-binding antibiotic, antiviral, antitrypanasomal and

anticancer agents can inhibit or disrupt such processes as DNA replication, transcription and topoisomerase activities. Chemotherapeutic agents bind to DNA within the grooves, ordinarily within the minor rather than the major groove, and/or by intercalating between the bases. Examples of clinically important intercalating-minor groove binders are daunomycin and the closely related adriamycin, currently two of the most widely used anticancer chemotherapeutic agents. However as a target for design of new chemotherapeutic agents, DNA offers special problems. Crystallography of DNA and its complexes is much less developed than that of proteins. The longest fragment of DNA solved by single crystal X-ray diffraction is less than 20 residues. In addition, modeling is difficult. With every residue in contact with aqueous solvent, the interface is much more extensive than with a globular protein. Modeling is further complicated by the high formal charge of DNA. Finally, the conformation of DNA is much more mutable than that of most protein targets. DNA conformation is highly dependent on that of the inhibitor. However, with the approaches described here, including our collaborations with groups in Paris and at Rutgers, we believe that the future prospects for this approach are encouraging.